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Asthma and Hay Fever

(Under the supervision of Richard Wiseman)

The Effect of Calcium Pantothenate on Induced Whealing and on Seasonal Rhinitis. Tuft, L., Gregory, J., and Gregory, D. C.: Ann. Allergy **16**: 639, 1958.

Pantothenic acid, which is an integral part of coenzyme A, is definitely related to the function of the adrenal cortex. In view of a previous report of favorable results in the treatment of allergic diseases with pantothenic acid and with vitamin B, of which pantothenic acid is a part, an investigation was made of the effect which this drug might have upon direct and indirect skin tests and upon clinical allergy.

Direct skin test reactions to pollen antigens and histamine were definitely reduced in size following the ingestion of pantothenic acid. When the drug was given regularly 4 times daily for a week and the patient was tested 4 hours following the ingestion of the last dose, there was only slight reduction in the reactivity of the skin. When the patient was tested one hour following the ingestion of the drug, however, there was a decidedly greater reduction in the skin reaction. It was also noted that with larger doses of pantothenic acid a more marked diminution in the skin reactivity occurred. The effect of the drug upon the nonspecific histamine reactions was not so decided as its effect upon the specific skin reactions to pollen antigens. Passive transfer reactions were affected in the same manner as direct tests. Coincidentally, with the reduction in skin test reactions a definite reduction in blood eosinophiles was also noted. This reduction compared favorably with that produced by the administration of other antiallergic remedies, such as cortisone, ACTH, antihistaminics, and epinephrine.

The double-blind technique was used to evaluate the clinical effect of the drug on a group of 19 seasonal hay fever patients. Each was given (1) an antihistaminic, (2) lactose, and (3) calcium pantothenate (150 mg. 4 times daily) during the height of the pollen season. Only 2 patients reported good results during the time they were taking the calcium pantothenate. No striking difference was noted in the results obtained with lactose and with calcium pantothenate, whereas the antihistaminic afforded relief in a fairly large number of patients. In view of the fact that calcium pantothenate inhibited skin reactivity, particularly with high dosage, the authors conjecture that the failure to obtain clinical relief may have been due to inadequate dosage. H. F.

Physical Conditioning Program for Asthmatic Children. Scherr, M. S., and Frankel, L.: J. A. M. A. **168**: 1996, 1958.

A program of physical conditioning was devised for a group of 25 asthmatic children in an attempt to improve their respiratory capacities and to develop their initiative and self-confidence. The group met two afternoons each week at the local Y.M.C.A. under the direction of a physical fitness director. The program included (1) basic techniques of abdominal and diaphragmatic breathing, (2) postural exercises, (3) gymnastics, and (4) adaptation conditioning. For the latter purpose, the principles of judo are employed to build up the child's confidence and to train him to handle aggressive situations. The general atmosphere of the program was one of play rather than of medical treatment. The child was taught to concentrate on improving his own ability rather than on competing with his neighbor. The program appeared to be beneficial to the participants. M. C.

Ethylnorepinephrine: A Unique Bronchodilator. Christensen, J. M., Valasec, F. E., and Tainter, M. L.: Am. Pract. **9**: 916, 1958.

The authors reviewed 34 articles concerning ethylnorepinephrine. This sympathomimetic drug was as effective a bronchodilator as epinephrine but produced fewer side effects. It must be administered parenterally. It did not cause an increase in blood pressure or cardiac work. Compared to ephedrine, amphetamine, and epinephrine, it did not have as great analeptic powers and its toxicity was extremely low, particularly as compared to epinephrine. Less frequent and less severe side effects, such as precordial

pain, nausea, and vomiting, were encountered with ethylnorepinephrine than with epinephrine. The results obtained in bronchial asthma with ethylnorepinephrine were comparable to those obtained with epinephrine, except in cases in which the asthma was complicated by bronchial infection. Children tolerated this drug better than epinephrine. H. F.

Dermatology

(Under the supervision of Monroe Coleman)

Dermatitis of the Face Caused by Guanine in Pearly Nail Lacquer. Stritzler, C.: Arch. Dermat. **78**: 252, 1958.

Four patients with a patchy eczematoid dermatitis of the eyelids, face, chin, and neck, who showed negative patch test reactions to ordinary nail lacquer, had positive reactions to pearly or frosted nail lacquer. Patch tests made with the individual ingredients in the nail lacquer, such as the solvent, plasticizer, resin, and pigment, also gave negative reactions, but tests made with the pearly material were positive. Since the pearly material is made from the fish scales of sardines and consists mainly of guanine, patch tests were performed with pure powdered guanine and powdered defatted sardine fish scales. Positive reactions were obtained with oil of these substances in the 4 patients, and negative responses were observed in 20 control subjects. All the patients were able to tolerate ordinary nail lacquer. Reactions to tests with sardine meat and the olive-oil extract of skinless and boneless sardines were negative. All four patients could eat sardines with or without scales with no untoward effects. None of these persons had handled or had had any previous contact with sardine scales or skins. Patch tests performed with chemicals similar to guanine, such as adenine, uric acid, caffeine, theobromine, and adenylic acid, were "all negative, suggesting that the NH_2 in the 2 position was essential to provoke the reaction." R. W.

Analysis of Protein Skin Reactivity in Infantile and Childhood Eczema. Ratner, B., and Collins-Williams, C.: A. M. A. Am. J. Dis. Child. **96**: 184, 1958.

The results of skin tests performed on 114 infants and children with eczema were analyzed. The group included 42 infants under 2 years of age, 38 older children with uncomplicated eczema, and 34 infants and children with eczema complicated by respiratory allergy. Each patient was scratch tested with 350 different allergens, and some were also tested intracutaneously with inhalants and pollens when the scratch tests to these allergens were negative. About 97 per cent of the group reacted to one or more allergens. Infants showed a high percentage of reactions to foods, while older children showed more reactions to inhalants. A higher percentage of infants than of older children reacted to foods alone. Although half of the children with uncomplicated eczema reacted to pollens, only 24 per cent of the infants showed positive pollen reactions. The vast majority of the infants and children reacted either to foods alone or to foods in combination with inhalants and pollens. As the infant grew older, the inhalant and pollen sensitivities increased in frequency, and it was necessary to do repeated tests in order to uncover these new sensitivities. In patients with eczema, the 10 allergens giving the greatest number of reactions, in decreasing order of frequency, were as follows: among the infants, egg, vegetables, inhalants, fish, fruits, meats, nuts, wheat, condiments, and milk; among the children, vegetables,

inhalants, fish, fruits, condiments, egg, nuts, bacteria, cereals, and wheat. Only 34 per cent of the patients with uncomplicated eczema showed pollen reactions, whereas 82 per cent of the patients with complicating respiratory allergy showed positive reactions to pollen. The incidence of positive reactions to egg decreased markedly as the patients became older. Sensitivity to a single food rarely occurred. Intracutaneous testing was resorted to for inhalants and pollens, since young children usually have such low-grade sensitivity to these substances that scratch tests fail to reveal their presence. The low incidence of positive reactions to chocolate, milk, and wheat is stressed, since these findings are contrary to the opinion of most allergists who regard these allergens as frequent offenders in eczema. The importance of inhalants and pollens as contributing factors in the eczema-respiratory syndrome is discussed. The writers confirm the fact that eczema frequently exists in conjunction with respiratory allergic disease. They conclude that the final evaluation of food sensitivity must rest on clinical corroboration of skin test reactions. R. W.

Perfume Dermatitis. Klarmann, E. G.: Ann. Allergy **16**: 425, 1958.

Allergic sensitivity to perfume has long been an accepted fact, but little work has been done to establish the exact nature of the processes involved. The author points out the specific nature of certain of the sensitizing chemicals found in perfume and the cross reactions which may occur with chemically and botanically related substances. A large number of essential oils are known to be factors in the development of allergic dermatitis and cheilitis. Perfumes may also act as inhalant allergens and produce upper respiratory symptoms. To date, little is known concerning the irritant and sensitizing potential of perfumes and perfume ingredients or of the concentrations in which these potentials become manifest in the form of clinical dermatitis. Little is also known concerning the existence of sensitizing synergisms or antagonisms of groups of materials found in perfumes, such as floral and essential oils and aromatic synthetics. The fixation of a perfume to the skin by means of some vehicle, such as a cream, a lipstick, or a face powder, may have a markedly different effect upon the skin than the transitory application resulting from a perfume or a toilet water. The absorption of essential oils by the skin may be an important factor in these problems. Although most cosmetic chemists have attempted to eliminate allergenic or sensitizing ingredients from their products, the presence of perfume is still a common and quite likely source of sensitization. H. F.

Chromate Sensitivity. Differentiation of Specific and Nonspecific Positive Patch Tests. Gaul, L. E.: Ann. Allergy **16**: 435, 1958.

A series of 844 patients was patch tested with a 1 per cent solution of potassium chromate. There were 667 negative reactions and 77 positive ones. The positive reactions were of three types: (1) erythematous reactions, (2) urticarial reactions, and (3) eczematous reactions. The first two types of positive reactions were found to be nonspecific in nature and occurred in those patients who showed, on further investigation, specific reactions to other organic or inorganic materials. The nonspecific reactions persisted for a much shorter period of time than did the specific reactions and appeared to be merely indicative of a hyperreactive state of the skin. The eczematous reactions, on the other hand, were specific in nature and consisted of either a flare of erythema with papules or more commonly, of frankly vesicular

lesions which often were weepy and pruritic in character. The most important characteristic of the specific reactions to potassium chromate was the duration of healing time, which averaged from 2 to 6 weeks. H. F.

The Use of Impatiens Biflora (Jewelweed) in the Treatment of Rhus Dermatitis. Lipton, R. A.: Ann. Allergy **16**: 526, 1958.

Impatiens biflora, or jewelweed, is an old-fashioned galenic, which has emetic, cathartic, and diuretic properties when taken internally. The author used a 1:4 dilution of the tincture of jewelweed for the local treatment of Rhus dermatitis. One hundred fifteen patients with Rhus dermatitis were divided into two groups. One group was treated with jewelweed alone, while the second group was treated with jewelweed on some areas and with other medications, such as calamine-menthol mixture, Burrow's solution, and hydrocortisone ointment on other areas. One hundred eight patients had an excellent response to the topical application of the jewelweed and were entirely free of symptoms within 2 or 3 days after the institution of treatment. Only 50 per cent of the patients who were treated with the other medications reacted favorably, and then only after a week or more of treatment. The 50 per cent of patients who failed to respond after a full week of treatment were then treated with jewelweed, with subsequent rapid improvement. The 7 patients who failed to respond to the jewelweed treatment were subsequently treated with parenteral ACTH or oral corticosteroids, with very good results. For further evaluation of the effectiveness of the jewelweed tincture on Rhus dermatitis, the author produced linear lesions of poison ivy on his own arms and studied the effects of the various medications. He confirmed the above findings, namely, that jewelweed was the most effective treatment. H. F.

Atopic Dermatitis: Role of Food Allergy. Morris, G. E.: Ann. Allergy **16**: 599, 1958.

Foods play a major role in the etiology of atopic dermatitis, particularly in infancy. Vomiting, "spitting up," "gas," diarrhea, and other gastrointestinal disturbances which follow the ingestion of a particular food may be evidence of food sensitivity. Eggs, wheat, and milk are the most common offenders. The use of diet diaries and questionnaires concerning food habits and reactions frequently yields important information. Botanical relationships between foods must be taken into account, and frequently an entire food family must be eliminated from the diet. In older children, inhalants, such as wool, house dust, feathers, animal danders, and pollens, must be regarded as possible causes of atopic dermatitis and proper measures must be instituted for their control. Bacterial agents and infections may adversely affect atopic skin conditions; staphylococcic vaccine can frequently be of help in the treatment of such cases. Local therapy in the acute stage should consist of soothing compresses or soaks along with colloidal baths but should never include ointments, pastes, or creams. The latter should be reserved for the subacute or chronic stages. When foods are eliminated from the diet, they should be eliminated completely (even to the avoidance of cooking or having these foods in the house) for periods of at least two to three months. Breast feeding is preferable for all infants, particularly for the children of atopic mothers. H. F.

Dermatitis Medicamentosa Due to Diuril (Chlorothiazide). Report of Three Cases. Rogin, J. R.: Arch. Dermat. **78**: 504, 1958.

Three patients developed erythematopapular and purpuric skin eruptions following the ingestion of chlorothiazide (Diuril). The lesions were confined

to the extremities in 2 patients and also involved the trunk in the third. The dermatitis developed 10 days following the ingestion of the medication in 2 cases. The third patient had been taking the diuretic intermittently over a 6-month period but had received 500 mg. daily for 8 days before the eruption finally developed. A review of each patient's history indicated that chlorothiazide was probably the offending factor. In each case, the eruption subsided when the medication was discontinued. An erythematopapular pruritic eruption on the extremities was the most prominent finding, although a considerable amount of edema of the involved areas was also present. R. W.

The Effects of Triamcinolone (Aristocort) and 6-Methylprednisolone (Medrol) on Some Skin Diseases. A Therapeutic Note. Kalz, F.: Canad. M. A. J. **79**: 400, 1958.

Triamcinolone (Aristocort) was used in the treatment of 48 patients with various skin disorders, which included 24 cases of atopic dermatitis. Twenty-one of the patients had previously been taking an average dose of approximately 15 mg. of prednisolone daily. A majority of the patients obtained a satisfactory therapeutic response with a daily maintenance dose of 6 mg. or less of triamcinolone. Four patients experienced epigastric distress, and several others had headaches, dizziness, drowsiness, leg cramps, or hyperhidrosis. Six patients who did not tolerate Aristocort were able to take 6-methylprednisolone (Medrol) effectively. It appeared that triamcinolone (Aristocort) may be superior to prednisolone in the steroid therapy of chronic dermatoses.

R. W.

Miscellaneous Allergies

(Under the supervision of Eugene Walzer)

Procaine Sensitivity: The Relationship of the Allergic Eczematous Contact-Type to the Urticarial, Anaphylactoid Variety. The Use of Xylocaine in Procaine-Sensitive Individuals. Fisher, A. A., and Sturm, H. M.: Ann. Allergy **16**: 593, 1958.

Procaine sensitivity represents an occupational hazard of considerable importance to the dental profession, and it is also fairly common among the general population. Many persons who have allergic eczematous sensitivity to products of the group embracing paraphenylenediamine, benzocaine, and para-aminobenzoic acid frequently show cross-reactions to procaine. Paraphenylenediamine and benzocaine are potent sensitizers, and it is possible that procaine sensitivity may become established in many patients who have never had actual topical contact with this drug. The capacity of procaine to induce urticarial, anaphylactoid allergy has never been adequately demonstrated. There have been some reports suggesting the occurrence of anaphylactoid reactions following the injection of procaine. One of these described a patient who reacted with collapse, choking, and angioneurotic edema following the injection of procaine. In an effort to determine more accurately the hazards of injection or ingestion of procaine in patients with allergic eczematous sensitivity to this material, 20 patients with strongly positive reactions to patch tests with 2 per cent procaine hydrochloride were studied. Each patient was tested in the following manner:

1. A scratch test with one drop of 2 per cent procaine hydrochloride was performed.

2. An intracutaneous injection of 0.1 c.c. of 2 per cent procaine hydrochloride was used.
3. A subcutaneous injection of 1.0 c.c. of 2 per cent aqueous procaine hydrochloride was injected in the deltoid area.
4. Each patient ingested 250 mg. of powdered procaine hydrochloride and 150 mg. ascorbic acid in capsule form three times a day for one week.
5. In addition, each patient was patch-tested with 2 per cent aqueous Xylocaine (lidocaine hydrochloride).

Patch tests with procaine yielded positive reactions in each instance. Neither systemic reactions nor whealing followed the scratch tests or the intracutaneous tests. Subcutaneous injection also failed to produce any evidence of systemic reaction, but two patients developed pruritic, tender nodules three days after the injection. The ingestion of procaine three times daily for one week also failed to produce any suggestion of a reaction. In none of the 20 procaine-sensitive patients in this series was there a positive patch test reaction to 2 per cent Xylocaine solution. These studies seemed to indicate that a vascular, urticarial type of sensitivity rarely accompanies an eczematous sensitivity to procaine. Since Xylocaine does not cross-react with procaine, it would appear to be an excellent substitute for local anesthesia, particularly for those dentists who have developed a contact type of reaction to procaine and for those patients, either atopic or nonatopic, with a history of eczematous procaine sensitivity. H. F.

The Effect of Tuberculin on Peritoneal Exudate Cells of Sensitized Guinea Pigs in Surviving Cell Culture. Waksman, B. H., and Matoltsy, M.: J. Immunol. **81**: 220, 1958.

The former concept that in tuberculin sensitivity necrosis regularly follows contact of the sensitive cells with the antigen (tuberculoprotein) has been challenged by more recent experiments which indicate that, under suitable experimental conditions, the sensitive cells may be stimulated instead of destroyed by such contact. With original techniques, the writers were able to show that washed sensitive peritoneal exudate cells responded to antigen contact by enhanced survival, a tendency toward maturation to large cells of typical macrophage morphology, and other characteristics which did not appear in the absence of antigen. The washed peritoneal exudate cells of tuberculin-sensitive guinea pigs and of normal control animals were kept at 37° C. in standing tubes in a culture medium containing 20 per cent normal homologous serum and varying concentrations of Old Tuberculin, glycerine, and P.P.D. Studies included direct microscopy, total viable cell counts, vital staining, and differential counts.

In the tubes containing antigen there was a definite, though often slight, fall in total cell count for the first 18 hours. This was followed by a pronounced late rise (72 to 90 hours) as compared to control cells not in contact with antigen. The antigen-treated cells showed an enhanced survival, as judged by changes in size, motility, adherence to glass, and dye ingestion, at a time when the control cells were dying. In the early stages, the large macrophages present at the start tended to disappear. Later there was an acceleration of maturation of many of the "intermediate mononuclear" cells toward large macrophage formation. The possible significance of these findings is discussed. B. S.

Quantitative Study of Local Passive Transfer of Tuberculin Sensitivity With Peritoneal Exudate Cells in the Guinea Pig. Waksman, B. H., and Matoltsy, M.: J. Immunol. **81**: 235, 1958.

Peritoneal exudate cells obtained from tuberculin-sensitive guinea pigs were mixed with antigen and injected into the skins of normal guinea pigs. The effects of variations in the number of cells and amount of antigen employed, and of incubation of antigen-cell mixtures, were studied. Typical tuberculin reactions were produced in normal animals by the intracutaneous injection of the antigen-sensitive cell mixtures. Intracorneal injections produced opacities lasting 48 to 72 hours. This reaction could not be produced with control mixtures lacking one of the major components. Newborn recipients did not show the local passive skin reaction. This might be due to the inability of transferred cells to mature in this environment (Dixon and Weigle) preventing macrophage development and antibody formation. High concentrations of tuberculin (1:20 to 1:5) in the mixtures often inhibited the transfer phenomenon. Incubation of cells in the presence or absence of antigen resulted in negative transfers.

The antigen-sensitive cell reaction at the transfer site resulted in a volume increase of cells observed in the previously described cell culture experiments (see previous abstract) which could account for the size of the local reaction in the absence of participation of the cells of the recipient. B. S.

The Allergenicity of Erythromycin. Stryker, H., Siegel, B., and Grolnick, M.: Antibiotic Med. & Clin. Therapy **5**: 723, 1958.

Erythromycin was used to treat various types of infections in 210 atopic patients, many of whom received several courses of the antibiotic. No evidence of an allergic reaction to this drug occurred in any patient in this selected group. A group of this type is more prone to develop allergic reactions than a nonatopic group. A survey of the literature and other sources by the authors indicated that the incidence of allergic reactions to erythromycin is insignificant. It was concluded that severe, immediate allergic reactions do not occur following the administration of erythromycin. M. C.

Anaphylaxis

(Under the supervision of Harold Friedman)

Hemorrhagic and Necrotic Reactions in Guinea Pigs During Protracted Anaphylactic Shock. Stone, S. H., and Freund, J.: Proc. Soc. Exper. Biol. & Med. **99**: 333, 1958.

Guinea pigs sensitized to egg albumin (EA) by the intracutaneous route with the aid of paraffin oil adjuvants containing mycobacteria responded to large subcutaneous doses of EA with massive hemorrhagic reactions at the injection sites. This phenomenon did not occur when mycobacteria were omitted from the sensitizing procedure, even though these animals developed antibody titers and showed systemic reactions similar to the preceding group. In both groups, a subcutaneous eliciting dose of EA produced a protracted but usually nonlethal anaphylactic shock. If death did occur, it came after 8 to 23 hours. Quite different were the results in animals that had been sensitized only with EA in saline by intracutaneous injection. In such animals anaphylactic death was usual and occurred in from 39 to 66 minutes. Autopsy of

these animals showed a combination of the findings usually present in acute and slightly prolonged anaphylactic shock, such as pulmonary emphysema and intestinal hemorrhages. In these animals antibody titers, determined by the passive cutaneous anaphylaxis technique, were quite low as compared to the titers found in animals which developed protracted shock.

The fact that killed mycobacteria are an essential sensitization factor in producing the hemorrhagic reactions suggests that the sensitivity may be of the delayed type. However, the nature of the entire mechanism which leads to the hemorrhage is still unknown. Anaphylactic sensitivity and antibody titers are obviously not decisive factors in the phenomenon.

After intravascular injections of *S. typhosa* or *E. coli* endotoxins, tuberculous guinea pigs will develop hemorrhagic reactions at the sites of intracutaneous tests with tuberculin. An attempt was made to determine whether this hemorrhagic phenomenon was similar to that noted in relation to protracted anaphylactic shock. Animals sensitized to various protein antigens with techniques involving adjuvants containing *M. tuberculosis* were skin tested with PPD. When protracted anaphylactic shock was then induced in these animals, gross hemorrhages failed to develop at the sites of the tuberculin reactions. Gross hemorrhage did occur, however, at the tuberculin sites after the intravenous administration of endotoxins. B. S.

In Vitro Anaphylactic and Nonanaphylactic Responses of Organs of Immunized Guinea Pigs. Katsh, S.: J. Pharmacol. & Exper. Therap. **124**: 86, 1958.

With the aid of adjuvants, guinea pigs were sensitized with guinea pig testicular homogenate, guinea pig sperm, or ovalbumin. From 17 to 60 days later the animals were exsanguinated. In animals sensitized to guinea pig testis or to guinea pig sperm, Schultz-Dale tests resulted in contractions of ileum segments by the addition of guinea pig sperm. Rabbit, bull, and rooster sperm and ovalbumin had no effect. In 3 of 43 male guinea pigs sensitized to testis or sperm, minimal contractions were noted in preparations of vasa deferentia or seminal vesicles. These organs, rich in smooth muscle, did contract regularly and adequately on addition of acetylcholine or histamine. Ovalbumin-sensitized male animals showed no contractions of the ileum on addition of sperm to the tissue bath. Their ilea all responded to ovalbumin, but their vasa deferentia and seminal vesicles were unresponsive to ovalbumin. Of 10 females sensitized to ovalbumin, 2 uteri and ilea were found to react to homologous sperm; in all 10 instances the uteri and ilea contracted on the addition of ovalbumin.

Plasma cells and lymphocytes were not found in the vasa deferentia and seminal vesicles, but the ileum contained much lymphoid tissue and the uterus contained many lymphocytes. It is noted that "the presence of smooth muscle alone is insufficient to insure demonstration of anaphylaxis in the Schultz-Dale test." Mast cells were found in the male accessory apparatus so that the insensitivity of the vas deferens could not be attributed to lack of these cells, which are presumed to release histamine during antigenically induced contracture. It is postulated that antibodies are carried to or synthesized in organs by cells of the antibody series (plasma cells, lymphocytes). These cells, on contact with antigen, then release a factor which causes the muscle to contract. In vivo contracture of the male accessory organs and the slight contractures of these organs in vitro in 3 instances noted above were believed due to the effect of antigen on circulating lymphocytes. E. K.

Pharmacology, Physiology, and Pathology

(Under the supervision of Bernard Siegel)

Corticotrophic Activity of Human Plasma Constituents. Bethune, J. E., Despointes, R. H., Antoniades, H. N., and Nelson, D. H.: Proc. Soc. Exper. Biol. & Med. **97**: 69, 1958.

Separated human plasma fractions, prepared according to the method of Cohn and his associates, were studied for ACTH activity utilizing the bioassay techniques of Nelson and Hume. Timed, intermittent, adrenal venous blood collections were made from a catheter placed in the right lumbo-adrenal vein of anesthetized, hypophysectomized dogs following the injection of ACTH or of an unknown plasma fraction. The ACTH activity of the blood samples was evaluated with reference to the increase of 17-hydroxycorticosteroid output of the dog adrenal over the base line obtained when only saline was injected. Active plasma fractions and ACTH standards were compared statistically.

Three types of human plasma were employed for separation: (1) plasma collected from normal human donors; (2) plasma collected from normal human donors to which U.S.P. ACTH was added in vitro one week following collection; and (3) plasma obtained from patients and one normal donor following the intravenous infusion of ACTH. In each instance, ACTH activity was shown to reside principally in plasma Fractions II and III (composed of gamma globulins and beta lipoproteins) and occasionally in Fraction IV-1 (alpha globulins, cholesterol) and Fraction IV-4 (alpha and beta globulins). Since Fractions II and III contain protein molecules of low solubility, while pituitary ACTH has been shown to be a small polypeptide of high solubility, there is the possibility that ACTH, as it occurs in human plasma, has different physical properties and that, if it exists in the plasma as a polypeptide, it is probably in complex with a protein of high molecular weight. H. S.

The Effects of Sympathomimetic Drugs on Renal Vessels. Aviado, D. M., Jr., Wnuck, A. L., and DeBeer, E. J.: J. Pharmacol. & Exper. Therap. **124**: 238, 1958.

All commercially available sympathomimetic drugs were compared in dogs for their effect on renal blood flow when injected intravenously or into the renal artery. Renal blood flow was measured by a rotameter inserted in the renal artery. Constriction of renal vessels and diminution of renal flow were produced by levarterenol, epinephrine, phenylephrine, metaraminol, methoxamine, and naphazoline when injected either intravenously or into the renal artery. A second group of drugs, when injected intravenously, produced constriction of other systemic blood vessels and cardiac stimulation. The net result was that blood pressure rose and renal flow was not necessarily diminished despite the renal vascular constriction also produced. This group included ephedrine, phenylpropanolamine, hydroxyamphetamine, and the new pulmonary vasodilator, compound 45-50. A third group of drugs, including amphetamine, had no important action on the renal vascular bed but increased renal flow as a result of systemic pressor action. A fourth group, which included isoproterenol, possessed a renal dilator action; when injected intravenously, the general arterial depressor effect predominated and renal blood flow decreased. The relationship of chemical structure to the effects noted are tabulated. E. K.

Pulmonary Arteriosclerosis Due to Serotonin. Rossi, P., and Zamboni, L.: Nature **181**: 1216, 1958.

Serotonin (5-hydroxytryptamine and creatinine sulphate) was injected intramuscularly or intraperitoneally into rabbits every 12 hours for 25 days in two cycles with a waiting period of 35 days between the cycles. Microscopic examination of the lungs revealed varying degrees of fibrous elastic intimal hyperplasia of small arteries and arterioles which was often asymmetrical. Hyperplasia of endothelium was sometimes observed. Deposits of mucopolysaccharides in the subendothelial layers were demonstrated. Veins were not affected.

It has been suggested that sertonin acts as a histamine liberator and is able to induce degranulation and disruption of tissue mast cells. Furthermore, connective tissue formation caused by carcinoids and their metastases may be related to the degranulating effect of serotonin upon the mast cells. The authors suggest that tissue edema caused by serotonin precedes the release of water-binding mucopolysaccharides from cells. It is possible that a humoral mechanism plays a part in the etiology of pumonary arteriosclerosis, in which case such amines as serotonin and histamine may cause intimal lesions when their concentrations increase beyond physiologic limits. I. G.

Effects of Histamine, 5 Hydroxytryptamine and Epinephrine on Pulmonary Hemodynamics With Particular Reference to Arterial and Venous Segment Resistances. Gilbert, R. P., Hinshaw, L. B., Kuida, H., and Visscher, M. B.: Am. J. Physiol. **194**: 165, 1958.

Epinephrine, norepinephrine, histamine, and 5 hydroxytryptamine (5 HT), when perfused through the isolated dog lung produced constriction of the small pulmonary veins which resulted in increased pressure in this area. Histamine caused a greater resistance in the venous segment than in the arterial bed, while 5 HT usually increased the arterial more than the venous resistance. The lungs were perfused at constant flow while pressures were measured in the pulmonary artery (PA), left atrium (PV), and in either the pulmonary artery wedge position (PA_w) or a small pulmonary vein (PV_s). Changes in the PA-PA_w pressure drop indicated arterial resistance changes, and changes in the PA_w-PV pressure gradient indicated venous resistance. When the predominant resistance increase was on the arterial side the lung weight fell, probably due to the decreased amount of blood in the organ, whereas when there was greater increase in the venous resistance the lung weight increased. The latter is probably a result of increased capillary blood volume. H. F.

Comparison of Lysergic Acid Derivatives and Antihistamines as Inhibitors of the Edema Provoked in Rat's Paw by Serotonin. Doepfner, W., and Ceretti, A.: Arch. Internat. Allergy & Appl. Immunol. **12**: 89, 1958.

Rats were injected in one hind paw with serotonin or histamine. The local edema was measured every 15 minutes for 2 hours and compared to the other hind paw which was injected with saline. A more marked edema was induced with 1 μg of serotonin injected into a paw than with 200 times this amount of histamine. The serotonin edema could easily be blocked if the site had been injected subcutaneously one-half hour previously with various amide derivatives of lysergic acid, especially methyl derivatives of ergonovine or methylergonovine. The inhibitory effect of 8 antihistamine compounds was

tested by injecting them intravenously 30 minutes prior to the injection of serotonin into the paw. Only those compounds of the phenothiazine (especially chlorpromazine and promethazine) and piperidine groups exerted a marked inhibition of the serotonin edema when used in a dosage range which was between 100 and 1,000 times higher than the effective dose of the most potent lysergic acid derivatives. I. G.

Immunology

(Under the supervision of Eloise Kailin)

Studies on the Transfer of Lymph Node Cells. XII. The Effect of Anti-Rabbit-Leucocyte Serum on the Transfer of Antigen-Incubated Lymph Node Cells. Harris, S., Harris, T. N., and Farber, M. B.: J. Exper. Med. **108**: 411, 1958.

When rabbit blood leucocytes are incubated with Shigella antigen and injected into nonimmune recipient rabbits, the latter develop antibodies to Shigella. If the recipient rabbits are pretreated with leucocytes from the donor rabbit and then are injected with antigen-incubated leucocytes, antibody formation to Shigella is diminished. An immunologic reaction was suspected as the cause of this suppressive effect on the transferred leucocytes. Accordingly, recipient rabbits were irradiated to diminish their capacity to form antibodies. Then leucocytes from a donor rabbit were injected. Subsequently, antigen-treated leucocytes from the donor were injected into the recipient. In the animals so treated, Shigella antibody appeared in higher titer than in nonirradiated controls. Irradiation inhibited the effect of preinjected leucocytes.

Adult rabbits were injected in the hind foot pads with donor rabbit leucocytes. Four days later, the popliteal lymph nodes of the recipients were removed and made into a suspension. Antigen-incubated leucocytes from the donor rabbits and cells from the popliteal lymph nodes of the recipient rabbits were then injected on the same day into a second set of irradiated recipients. The secondary recipients under these conditions showed lower Shigella titers than the controls. The control animals had received the same treatment except for the heating of the popliteal cell suspension or they had received popliteal lymph node cells draining sheep erythrocyte depots instead of rabbit leucocyte depots. Thus, the "preinjection effect" was shown using antileucocyte antibody from lymph node suspensions.

Rabbits were immunized to rabbit leucocytes, and their sera were injected into recipients of antigen-incubated leucocytes. Such sera caused marked suppression of resulting antibody titers. When the antileucocyte sera were incubated with rabbit lymph node cells, their ability to interfere with antibody formation in the recipient was diminished and the resulting titers were increased. This effect resided in the globulin fraction of the serum. It is concluded that the suppression of appearance of antibodies in recipients of antigen-incubated leucocytes can be passively transferred by antileucocyte serum. The implications of these findings to graft rejection are discussed.

E. K.

Thyroid-Specific Autoantibodies Studied by Passive Cutaneous Anaphylaxis of Guinea Pig. Ovary, Z., Randall, H., Witebsky, E., Rose, N. R., Shulman, S., and Metzgar, R.: Proc. Soc. Exper. Biol. & Med. **99**: 397, 1958.

Thyroid-specific autoantibodies in animals and in patients with chronic thyroiditis have been demonstrated by tanned cell agglutination, precipitation,

and other techniques. In this report the subject was studied by means of passive cutaneous anaphylaxis in the guinea pig. The specificity and intensity of the reactions between thyroid autoantibodies and homologous and heterologous thyroid antigens were investigated.

It was demonstrated that human, rabbit, or guinea pig thyroid autoantibodies will produce positive PCA reactions when tested with corresponding homologous antigens (thyroid extract and purified derivative). There were no cross-reactions with antigens of other species.

Five human thyroiditis sera were studied. Only homologous thyroid preparations (human thyroid extract and thyroglobulin) completely neutralized the autoantibodies in these sera. Other human organ extracts or thyroid extracts of other species did not significantly affect these antibodies. Diiodotyrosine, triiodothyronine, and thyroxine did not neutralize human thyroid autoantibody. These results are indicative of the high degree of specificity which characterizes this antibody. The results obtained establish the feasibility of the PCA technique in the study of thyroid autoantibodies of rabbit, guinea pig, and man. B. S.

Elimination of Antigen-Antibody Complexes From Sera of Rabbits. Weigle, W. O.: J. Immunol. **81**: 204, 1958.

Antigen-antibody complexes, prepared in vitro with excess antigen, were injected intravenously into nonimmunized rabbits and their elimination rates were studied. Large antigen-antibody complexes left the circulation rapidly while smaller complexes circulated with an exponential half-life.

Following the intravenous injection into rabbits of soluble BSA-anti-BSA complexes, prepared in the region of antigen excess, part of the complexes was eliminated at once and part at an exponential rate with a half-life of about 2.7 days. For the BGG-anti-BGG complexes similarly prepared and administered, the exponential rate had a half-life of 1.8 days. In either system the elimination rate was faster than that for antigen or antibody when given alone. BSA-anti-BSA complexes, prepared at equivalence with nonprecipitating antibody, were eliminated in a few hours, whereas with complexes prepared in the region of excess of antigen the rate of elimination had a half-life of 2.3 days.

Complexes prepared at equivalence tended to fix rabbit complement and to be precipitated in its presence. Smaller complexes prepared in the region of large antigenic excess did not fix rabbit complement or precipitate in its presence. Complement may therefore play a part in the elimination of soluble antigen-antibody complexes.

It seems likely that in the in vivo response to antigenic stimulation the newly synthesized antibodies form small complexes with the antigen which is present in excess and circulate in the blood. As new antibody forms, it combines with the antigen present in these complexes, which increase in size until they are large enough to be removed. It would seem, therefore, that the elimination of these complexes depends to a considerable extent on the amount of antigen injected and the rate of antibody synthesis. B. S.

The Effect of Feeding Simple Chemical Allergens to Pregnant Guinea Pigs Upon Sensitizability of Their Offspring. Baer, R. L., Rosenthal, S. A., and Hagel, B.: J. Immunol. **80**: 429, 1958.

Groups of pregnant albino guinea pigs were force-fed olive oil solutions of picryl chloride (PC) or dinitrochlorobenzene (DNCB). Pregnant control

animals received only olive oil. When the offspring of these animals were fully grown they were sensitized to PC by intramuscular injection and topical application and to DNCB by topical application. After an interval of four weeks they were skin tested with various dilutions of PC and DNCB. The results were read after 24 hours. Some of the animals were subsequently sensitized and tested with citraconic anhydride (CA).

The offspring of the treated animals and of the controls were compared. The animals which had been exposed to PC and DNCB during fetal life showed a slightly, though consistently diminished, capacity to become sensitized to the homologous allergen. That this effect was specific was indicated by the fact that no such effect was noted with respect to CA sensitization of the offspring. Neither the test animals nor the control group had been exposed to CA during fetal life.

The results of this experiment were not considered to be conclusive but are sufficiently suggestive to warrant further study. D. G.

On Nonantigenicity of Polysaccharides in Guinea Pigs. Maurer, P. H., and Mansmann, H. C.: Proc. Soc. Exper. Biol. & Med. **99**: 378, 1958.

Purified preparations of polysaccharides have not been found to be antigenic in rabbits but they produce good antibody titers in human beings. The antigenicity of pneumococcal polysaccharide SIII and of dextran were studied in guinea pigs. Vigorous techniques for immunization were employed, including the use of various types of adjuvants and injections of antigen-antibody precipitates formed in the region of antibody excess. For the detection of antibodies in the serum, techniques included microprecipitation, agar diffusion, and passive cutaneous anaphylaxis. The results obtained in all of these experiments were uniformly negative for the dextran and polysaccharide antigens. Positive results were obtained in these animals with egg albumin and rabbit gamma globulin. The possible causes for lack of antigenicity of dextran and polysaccharides in the guinea pig are discussed. B. S.

Immunologic Differences Between Iso-antibodies and Auto-antibodies. Pirofsky, B.: Am. J. Clin. Path. **29**: 120, 1958.

A warm-acting, erythrocyte-coating material (E.C.M.) was obtained from the sera of 4 patients with acquired hemolytic anemia and leukemia. This material was not specific for any of the 20 red cell antigens studied and acted as panhemagglutinin. The Coombs' test was positive, indicating that the coating material was a globulin. Iso-antibodies were studied in two standard red cell systems. Mixtures of red cell antigens and antibodies (anti-Rh_o [d] and anti-rh′ [c]) in combination with various antihuman globulin serums showed inhibition of the action of incomplete iso-antibody and a lessened availability of anti-human globulin antibody. In contrast, when the materials used consisted of eluted E.C.M. material (auto-antibody), neither E.C.M. nor anti-human globulin seemed to be diminished in availability for further reaction. The addition of O, rh (cde) erythrocytes to this mixture permitted interaction and agglutination, so that the availability of both anti-human globulin and E.C.M. decreased. The responses of E.C.M. material to heat and to electrophoresis suggested that this material was a gamma globulin. The function of the erythrocyte which makes it essential to the reaction between E.C.M. and anti-human globulin is not known. E. K.

Isolation of Antibodies on Antigen-Polystyrene Conjugates. Gyenes, L., Rose, B., and Sehon, A. H.: Nature **181**: 1465, 1958.

Protein antigens were coupled through azo bonds to a nonpolar polystyrene framework. The insoluble Styron-antigen conjugates (prepared with human serum albumin, human serum gamma globulin, whole normal human serum, bovine serum albumin, or water-soluble extract of ragweed pollen) were able to remove precipitating antibodies from homologous rabbit antisera. Antibodies could be recovered from the Styron-antigen-antibody complexes by dissociation with hydrochloric acid at pH 3, and they retained their immunologic specificities.

Styron-ragweed conjugates were capable of removing completely skin-sensitizing and blocking antibodies from sera of ragweed-sensitive persons. This was taken as evidence that firm combination occurred between these antibodies and ragweed allergens. These antibodies were not removed by heterologous Styron-antigen conjugates, demonstrating the specificity of the combination between these antibodies and the appropriate allergens. I. G.

Leucocyte Antibodies in Sera From Pregnant Women. Van Rood, J. J., Eernisse, J. G., and van Leeuwen, A.: Nature **181**: 1735, 1958.

A patient who had had 6 pregnancies (2 abortions) was delivered of premature twins. She had post-partum bleeding for which a transfusion was given. Although there was no blood group incompatibility and no previous transfusion, a febrile reaction occurred. The patient's serum before transfusion agglutinated leucocytes from 11 of 12 normal donors but did not agglutinate her own leucocytes. After absorption with leucocytes from one donor the serum agglutinated only those of other donors, indicating that leucocytes from different donors differ in antigenic structure. Sera from patients with an average of 7 pregnancies contained leucocyte antibodies, whereas sera from patients with an average of only 3 pregnancies did not contain leucocyte antibodies.

It was suggested that leucocyte antibodies might influence a fetus unfavorably and that these antibodies might be the result of previous pregnancies without transfusion or that they may occur in a male from repeated blood transfusions. I. G.

Miscellaneous

(Under the supervision of Murray Albert)

Eosinophilic Granuloma of the Lung With Eosinophilic Pneumonia. Kaunitz, J.: New York J. Med. **58**: 1279, 1958.

A 55-year-old man developed an acute eosinophilic granuloma of the lung concomitantly with a Loeffler's type of pneumonic infiltration. Prior to this illness he had been in good health except for a mild case of mycosis fungoides of 7 years' duration. He had symptoms typical of a moderately severe respiratory infection, but after one month of treatment with penicillin and tetracycline he had not improved. A blood count at this time showed a 19 per cent eosinophilia. Sputum examination was negative for acid-fast bacilli, but x-ray examination of the lungs indicated cloudiness of both apices; consequently, the patient was placed on streptomycin, isoniazid, and para-aminosalicylic acid. He continued to run a downhill course and, after losing 20 pounds within the next 2 months, he was hospitalized. A blood count done

at this time revealed a mild anemia and a 15 per cent eosinophilia. Examination showed a few small nodules identified as mycosis fungoides and numerous physical signs in his lungs indicative of a pneumonic process. Chest x-rays at this time (4 months following the onset of his illness) showed diffuse involvement of the right lung, with the heart and trachea displaced to the right. Diagnostic tests for all types of specific lung disease were negative and skin tests with allergens gave negative results except for moderately positive reactions to penicillin and streptomycin.

Four and one-half months following the initial onset of the illness, 80 units of ACTH gel and 1,000 mg. of Mysteclin were administered daily. Within 24 hours, the temperature dropped to normal and there was marked symptomatic improvement. The patient continued to improve for the next 3 weeks, when he suddenly developed a severe epigastric pain. X-rays showed a pneumoperitoneum, and immediate laparotomy revealed a large perforated gastric ulcer. ACTH therapy was stopped immediately following surgery. Within a week, the patient's temperature had climbed back to 105 degrees and there was a recurrence of all previous symptoms. Since attempts to control his symptoms with various types of symptomatic medication, including Adrenaline, antihistamines, and antipruritics, were unsuccessful, he was given small doses of prednisone to which were added the appropriate drugs and diet for the prevention of further gastric complications. This medication was started after a lung biopsy had shown areas of granulomatous infiltration and pneumonic patches, both of which contained fibrin and eosinophils in large quantities. On the regime of steroids and antacids, the patient made an uneventful recovery and was discharged from the hospital one month later on a maintenance dose of 8 mg. of prednisone daily. Six months following hospitalization he had gained 20 pounds in weight and was working 8 hours each day. Tonsillectomy was performed 14 months following his initial illness, at which time a small peritonsillar abscess was accidentally discovered and opened. The patient was kept on steroid therapy for one year, remained in excellent health, and failed to develop symptoms after the hormone was stopped. X-rays of his lungs taken 2 years and 4 months following the onset of his illness were normal. The author suggests that the peritonsillar abscess may possibly have played a part in producing the acute allergic disease which caused such a severe lung reaction. He believes that the high eosinophil count indicates that this patient had an acute Loeffler's syndrome rather than an eosinophilic granuloma. The patient's remarkable recovery justified the continuing use of steroids with antacid therapy, in spite of the previous severe reaction to ACTH. R. W.